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Effect of short term water deprivation on the pharmacokinetics of Sulphadimidine in West African Dwarf (WAD) goats (*Capra hircus*)

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ABSTRACT

Background: Sulphadimidine, a synthetic antimicrobial drug is widely used in veterinary medicine in the treatment of animal diseases. The pharmacokinetics of sulphadimidine could be altered by water deprivation. *Objectives:* The present study was carried out to determine the effect of short term water deprivation on the pharmacokinetics of sulphadimidine in West African Dwarf (WAD) goats following intramuscular route of administration. *Materials and Methods:* In a randomized parallel study, eight (8) WAD goats comprising 4 males and 4 females were separated into 2 groups of 4 each. Sulphadimidine was administered at a dose of 100 mg/kg body weight to goats in group one, while the goats in group two were deprived of water for 3 days prior to sulphadimidine

administration on the right gluteal muscle. *Results:* The volume of distribution (Vd) (12.51±0.85 L/kg) and total body clearance (Cl) (2.11±0.15 L/kg/h) of the non-water deprived WAD goats were significantly higher ($p<0.05$) in comparison with the Vd (5.27±0.47 L/kg) and Cl (0.83±0.20 L/kg/h) of the water deprived WAD goats. The mean residence time (MRT) (5.38±0.52 h), area under the plasma concentration versus time curve from 0 to 48 h (AUC_{0-48}) (734.92±88.32 µg/ml.h) and area under the moment curve (AUMC) (4075.43±778.53 µg/ml/h^2) were significantly ($p<0.05$) lower in the non-water deprived WAD goats in comparison to the MRT (7.67±1.11 h), AUC_{0-48} (1101.96±183.08 µg/ml.h) and AUMC (8987.01±2577.86 µg/ml/h^2) of water deprived WAD goats. *Conclusion:* The pharmacokinetic parameters were altered in the water deprived goats due to reduced distribution of sulphadimidine to tissues and slower elimination from the body due to dehydration. This should be considered during therapy to optimize therapeutic outcome.

Keywords: Sulphadimidine, Pharmacokinetics, West African Dwarf goats, Water deprivation.

1. INTRODUCTION

Dehydration in animals may occur as a result of water deprivation which may be caused by factors such as human negligence, disease states such as polyuria, diarrhea, esophageal and pyloric obstructions and exposure to high and extreme temperatures [1]. Dehydration could result in significant decrease in body weight due to decrease in feed consumption to prevent elevations in extracellular fluid osmolarity and sodium concentrations [2-4]. Dehydration causes physiological and biochemical changes which could affect the pharmacokinetics of drugs.

Sulphadimidine, a systemic sulphonamide is widely used in veterinary medicine in the treatment of animal diseases including norcardiosis, actinomycosis, chlamydiosis, toxoplasmosis and coccidiosis [5-6]. Sulphonamide drugs were the first antimicrobials to be used systemically, and paved way for the antibiotic revolution in medicine. They are continually being used because of their low cost and effectiveness.

The pharmacokinetics of sulphadimidine has been reported in cows, goats, dogs, broilers and turkeys [7-11]. The present study was carried out to determine the effect of short term water deprivation on the pharmacokinetics of sulphadimidine in West African Dwarf (WAD) goats following the intramuscular route of administration.

2. MATERIALS AND METHODS

Experimental animals

This study was conducted in the Department of Veterinary Pharmacology and Toxicology, College of Veterinary Medicine, Federal University of Agriculture Makurdi. The West African Dwarf (WAD) goats were purchased from local breeders in Makurdi metropolis. They were screened for the presence of endo and ectoparasites and vaccinated against *Pest des Petits Ruminants* (PPR) and stabilized for two weeks prior to experimentation. The animals were fed on pasture and concentrate. Water was provided *ad libitum*. All the animals were handled according to the international guiding principle for biomedical research involving animals [International Council for Laboratory Animal Science [ICLAS] and Council for International Organization of Medical Sciences (CIOMS) [12], as permitted by the College of Veterinary Medicine, Federal University of Agriculture, Makurdi, Ethical Committee.

Experimental design and drug administration

Eight (8) WAD goats aged 1 year were separated into two groups of four animals consisting of two males and two female goats each. The goats in group one weighed 10.50±1.53 kg while the goats in group 2 weighed 9.25±1.52 kg before water deprivation and 8.50±1.43 kg after 3 days of water deprivation. The animals were fed on pasture and concentrate. Water was provided *ad libitum* to the animals in group one while those in group two were deprived of water for three days prior to sample collection and until after collection of samples. Sulphadimidine sodium (33.3%) (Shijiazhuang Guanghua Pharma. Co, Ltd. China) was administered into the right gluteal muscle of the goats at a dose of 100 mg/kg body weight.

Blood sample collection

Blood samples (2.0 ml) were collected through the left jugular vein of each goat prior to sulphadimidine administration and at these time periods post drug administration 15, 30, 45 min and 1, 2, 4, 6, 8, 10, 12, 24, 48 hr. The samples were collected using 23 G disposable needle and 2 ml syringe into heparinized tubes. The samples collected were centrifuged at 3000 rpm for 10 min and the plasma obtained and stored at -20°C until analysed.

Determination of sulphadimidine in plasma

Plasma concentration of sulphadimidine was determined by a modified chemical assay method [13]. The method is based on the diazotization of sulphadimidine and coupling with 8-OH quinoline (Sinopharm, China) in alkaline media to yield red coloured products with absorption maxima at 500 nm. The procedure is briefly described below.

To 0.4 ml of plasma in a 5 ml glass test tube, 2 ml of distilled water was added, followed by 0.6 ml of 20% trichloroacetic acid (Guangdong, China). The resulting solution was mixed using a vortex mixer and centrifuged for 5 min. To the clear supernatant (2.5 ml), 0.15 ml of 1.0% sodium nitrite (Kermel, China) was added, mixed and allowed to stand for 5 min. Then 0.25 ml of 2.0% sulphamic acid (BDH Chemicals, England) was added, mixed and allowed to stand for 5 min. This was followed by addition of 0.2 ml of 0.5% 8-OH quinoline (Sinopharm, China). The resulting solution was mixed and allowed to stand for 5 min, followed by addition of 0.2 ml of 20% sodium hydroxide (Qualikems, India). The resulting solution was mixed and the absorbance read using a UV-spectrophotometer (spectrum lab 23A, 340- 1000 nm) at a wavelength of 500 nm.

The linear calibration curve of sulphadimidine in plasma within the range of 1.25-20.0 µg/ml was obtained by plotting absorbance on y-axis against time on x-axis. The calculation of the linear regression showed R^2=0.998. The limit of detection (LOD) and limit of quantification (LOQ) of sulphadimidine in plasma were 0.08 and 0.24 µg/ml respectively. The intra-day and inter-day precision were 0.50 and 0.80 % respectively.

Calculation of pharmacokinetic parameters

The pharmacokinetic parameters for individual animals were calculated using established pharmacokinetic equations [14-16] and pharmacokinetic software (Kinetica 5.0, Thermo Fischer Scientific). Micro (α, β) constants were determined from all the plotted graphs obtained from the generated data.

Statistical analysis

The data on plasma kinetics and pharmacokinetic parameters were presented in graphical and tabular form respectively. Plasma concentrations and pharmacokinetic parameters were presented as Mean±Standard Error of Mean (SEM) and analyzed by Student's t test paired using Graph Pad Prism 6.03 for windows at 5% level of significance.

Table 1 Pharmacokinetic parameters of sulphadimidine in non-water deprived and water deprived WAD goats following intramuscular treatment at 100 mg/kg body weight (n=4).

Kinetic parameters	Non-water deprived WAD goat	Water deprived WAD goat
Cmax(µg/ml)	106.50±3.98	102.56±5.07
Tmax(h)	1.62±0.23	1.75±0.14
α (1/h)	1.36±0.06	1.03±0.38
$T_{1/2\alpha}$ (h)	0.48±0.03	0.94±0.41
MAT (h)	0.85±0.15	1.36±0.59
β (1/h)	0.17±0.01	0.15±0.02
$T_{1/2\beta}$(h)	4.08±0.23	4.90±0.75
Vd(L/kg)	12.51±0.85	5.27±0.47[a]
Cl(L/kg/h)	2.11±0.15	0.83±0.20[a]
MRT(h)	5.38±0.52	7.67±1.11[a]
AUC_{0-48}(µg/ml.h)	734.92±88.32	1101.96±183.08[a]
$AUC_{0-\infty}$(µg/ml.h)	745.41±90.26	1110.49±182.10[a]
AUMC(µg/ml.h^2)	4075.43±778.53	8987.01±2577.86[a]

Data are presented as mean±SEM; a=p<0.05, paired student's t test.

Cmax, maximum concentration; Tmax, time of maximum concentration; α, absorption rate constant; $T_{1/2\alpha}$, absorption half life; β, elimination rate constant; $T_{1/2\beta}$, elimination half life; Vd, volume of distribution; Cl, total body clearance; MRT, mean residence time; AUC_{0-48}, area under the plasma concentration vs time curve from 0 to 48 h; $AUC_{0-\infty}$, area under the plasma concentration vs time curve from 0 to infinite; AUMC, Area under the moment curve.

3. RESULTS

The pharmacokinetic parameters of sulphadimidine in non-water deprived and water deprived WAD goats following a single intramuscular administration of sulphadimidine at a dose of 100 mg/kg body weight are shown in table 1. Plasma concentrations of

free sulphadimidine were detected for 48 h. The kinetic disposition of the sulphadimidine indicated that the data best fit a two compartmental open model (fig. 1).

The volume of distribution (Vd) (12.51±0.85 L/kg) and total body clearance (Cl) (2.11±0.15 L/kg/h) of the non-water deprived WAD goats were significantly higher ($p<0.05$) in comparison with the Vd (5.27±0.47 L/kg) and Cl (0.83±0.20 L/kg/h) of the water deprived WAD goats (table 1).

The mean residence time (MRT) (5.38±0.52 h), area under the plasma concentration versus time curve from 0 to 48 h (AUC_{0-48}) (734.92±88.32 µg/ml.h), area under the plasma concentration versus time curve from 0 to infinite ($AUC_{0-\infty}$) (745.41±90.26 µg/ml.h) and area under the moment curve (AUMC) (4075.43±778.53 µg/ml/h^2) were significantly ($p<0.05$) lower in the non-water deprived WAD goats in comparison to the MRT (7.67±1.11 h), AUC_{0-48} (1101.96±183.08 µg/ml.h), $AUC_{0-\infty}$ (1110.49±182.10 µg/ml.h) and AUMC (8987.01±2577.86 µg/ml/h^2) of water deprived WAD goats (table 1).

However, other kinetic parameters including the maximum concentration (Cmax), time of maximum concentration (Tmax), absorption rate constant (α), absorption half life ($T_{1/2\alpha}$), mean absorption time (MAT), elimination rate constant (β), and elimination half life ($T_{1/2\beta}$), were not significantly different ($p>0.05$) between the two groups (table 1).

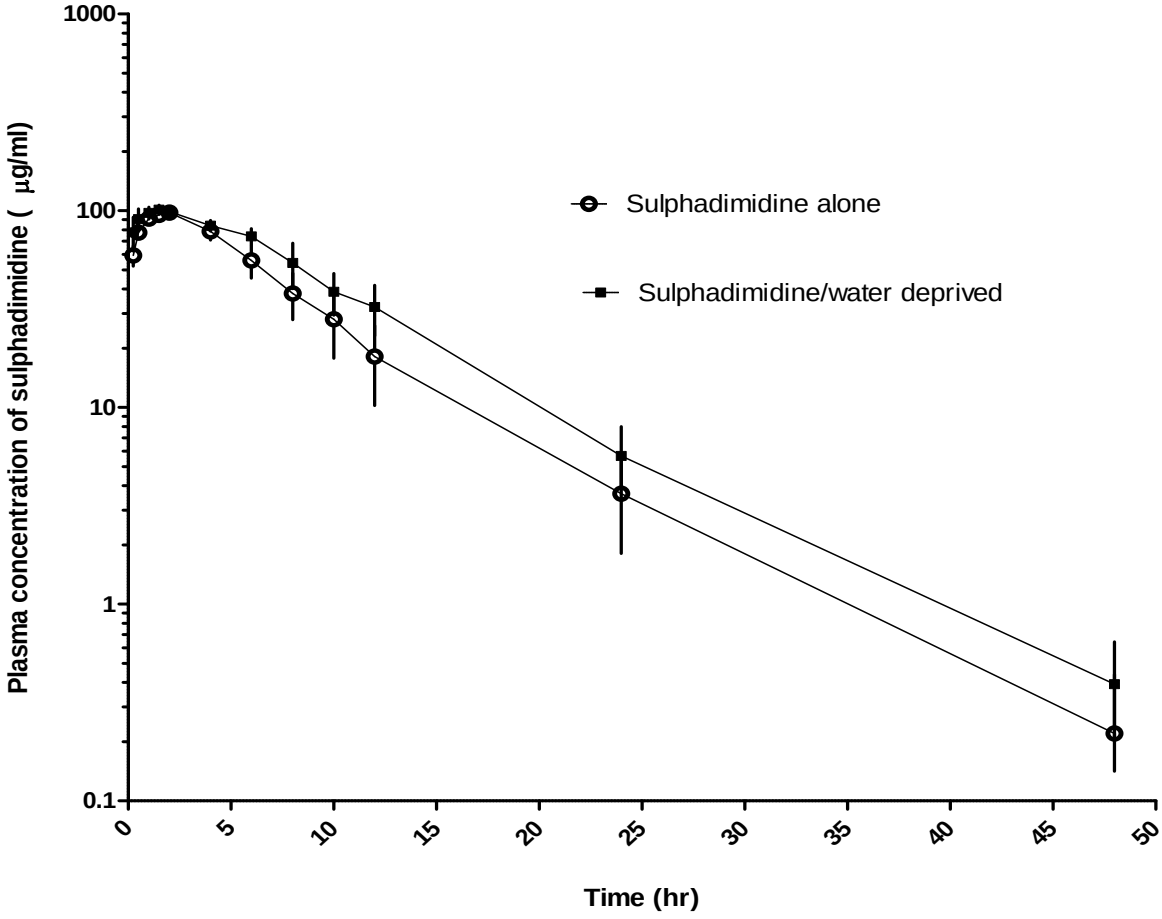

Fig 1: Mean plasma concentrations of sulphadimidine (µg/ml) in non-water deprived and water deprived WAD goat following intramuscular treatment at 100 mg/kg body weight (n=4).

4. DISCUSSION

Water deprivation for 3 days resulted in an 8.11 % change in body weight ($p<0.05$) between the non-water deprived and water deprived WAD goats. This is in agreement with the report of Igbokwe [17] that water deprivation results in loss of body weight due to loss of body water and fat. Sulphadimidine administered intramuscularly at a dose of 100 mg/kg body weight in this study resulted in measurable blood level for 48 h in both non-water deprived and water deprived WAD goats (table 1). The result also indicated that sulphadimidine was eliminated from the plasma in a biphasic process following intramuscular administration in both groups (fig.1). This agrees with the findings of Akogwu *et al.* [11]. The findings are at variance with the reports of Elsheikh *et al.* [18]

and Elsheikh *et al.* [19]. The reason for the variance may be due to differences in the route of administration because Elsheikh *et al.* [18] administered sulphadimidine intravenously.

Water deprivation in the present study resulted in a significant increase ($p<0.05$) in Vd (12.51±*0.85* L/kg) and Cl (2.11±*0.15* L/kg/h) in non-water deprived WAD goats in comparison with the water deprived WAD goats where Vd and Cl were 5.27±*0.47* L/kg and 0.83±*0.20* L/kg/h respectively (table 1). The volume of distribution (Vd) relates the drug level in the plasma to the total amount of drug in the body after absorption and attainment of distribution equilibrium. The higher Vd observed in non-water deprived goats would be an indication of the more extensive distribution in non-water deprived goats compared to water deprived goats. Water deprivation is known to decrease total body water, blood and plasma volumes, extracellular and intracellular fluid volumes [20-23]

Total serum or plasma proteins and albumin concentrations are known to increase with water deprivation [22, 24, 25]. The increased plasma albumin as a result of water deprivation could increase drug protein binding and thereby preventing more extensive distribution of the drug especially intracellular and this could be a factor in volume of distribution of sulphadimidine observed in water deprived goats in the present study as compared to that of non-water deprived goats.

The observed higher elimination half-life (4.90±0.75 h) and mean absorption time (1.36±0.59 h) in water deprived goats compared to that of non-water deprived goats ($T_{1/2\beta}$=4.08±0.23 h; MAT=0.85±0.15 h) are in agreement to the behavior of antipyrine in water deprived camels [26]. However, the higher elimination half-life and MRT observed in water deprived goats in the present study are in contrast to the observation of Etuk and Onyeyili [27] in water deprived goats administered chloramphenicol intravenously and deprived of water for 24 hours. The observed difference could be due to the difference in the route of administration and the degree of water deprivation. In the present study goats were deprived of water for 3 days. It has been observed that water deprivation and its associated pathophysiological changes could differ in short and long term conditions. Serum urea concentrations were observed to increase in sheep [28] and in goats [29] after short term water deprivation, but following prolonged period of water deprivation, the serum urea concentration returned to normal [17] or decreased [30]. The lower body clearance values of water deprived goats may have resulted from the decreased concentration of the free drug in the blood and subsequently to the kidney and other organs of elimination due to inadequate blood volume [17]. Decrease blood volume as a result of water deprivation also may explain the higher concentration of the drug in water deprived goats compared to the non-water deprived goats.

Dehydration has been known to cause significant decrease in blood volume and a reduction in hepatic enzymes activity [31]. This may account for the decrease in the Vd and Cl of sulphadimidine in the water deprived goats. This findings agrees with the report of Elsheikh *et al.* [19] following 12 % water deprivation in Nubian goats, Ziv *et al.* [32] in dehydrated camels treated with gentamicin and Hunter *et al.* [33] in pneumonic sheep treated with gentamicin.

In conclusion, water deprivation resulted in reduced body weight due to reduced feed intake in WAD goats. The pharmacokinetic parameters were altered in the water deprived goats due to reduced distribution of sulphadimidine to tissues and slower elimination from the body due to dehydration. This should be considered during therapy to optimize therapeutic outcome.

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Competing interest

Authors have declared that there is no competing interest

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